

## **REMARKS**

This Amendment and Reply seeks to place this application in condition for allowance. Certain claims have been amended to more clearly describe the invention, to improve grammar, to correct inadvertent typographical errors, and to address the Examiner's concerns regarding clarity. No new matter has been added.

All of the objections and rejections raised in the Office Action of October 19, 2005 (hereinafter the "Office Action") have been addressed in detail below.

### **Amendments to Independent Claims**

Briefly, Applicants have amended independent claim 1 to include "a plurality of beads or particles". Independent claim 1 was amended to further recite that "the second radiation converting component is embedded in or attached to at least one of the plurality of beads or particles" and "the plurality of beads or particles is embedded in the macroporous matrix".<sup>1</sup> These amendments are fully supported by the specification as filed. See, for example, page 10, lines 1-9. No new matter has been added.

### **Claim Rejections – 35 USC §112**

In paragraph 3 of the Office Action, claim 80 was identified as being indefinite. Applicants have amended claim 80 to address the concern raised in the Office Action. No new matter has been added.

### **Rejection of the Claims – 35 USC § 103**

In the Office Action, all of the claims were rejected as being unpatentable over Chick et al. (U.S. Patent 6,040,194) and Noronha et al. (U.S. Patent Application Publication US

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<sup>1</sup> Independent claims 71 and 102 have been amended in similar manner.

2002/0197724) alone or in view of other U.S. patents. Applicants respectfully disagree.<sup>2</sup> However, in an effort to expedite and simplify the prosecution, Applicants have amended the independent claims as mentioned above.<sup>3</sup>

In an effort to present a more concise response, the remarks below focus on some of the patentable aspects of the amended independent claims. No inference or conclusion should be drawn that Applicants' response to this rejection is exhaustive. Indeed, the reasons set forth below are *not* the only reasons the independent claims are patentable over Chick and Noronha, whether alone or in combination with the other art of record.

Notably, as for the rejected original claims, no inference or conclusion should be drawn that Applicants believe that such claims (independent or dependent) were unpatentable in view of the instant amendment notwithstanding this amendment.

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<sup>2</sup> As discussed in detail below, Applicants respectfully disagree with the position that a person of ordinary skill in the art would implement certain aspects of the Noronha sensor into the sensor of Chick. The Noronha photo-induced electron transfer type sensor and the Chick fluorescence resonance energy transfer type sensor are quite different sensors. These sensors are based on very different sensing techniques. In this regard, the sensors function and/or respond to the presence of analytes in an entirely different manner. One skilled in the art would not substitute the features of one of the sensors into the other sensor and anticipate that such feature would be operative therein. In this regard, there is no evidence in the Office Action to support the position that "it would have been obvious to one having ordinary skill art ... to include in the device of Chick et al., a radiation converting component wherein the efficiency of conversion is independent of the concentration of analyte as taught by Noronha et al., in order to provide an internal referencing system to correct for background fluorescent signals and cancel out changes in fluorescence intensity." (Office Action, pages 4-5). Importantly, a general relationship between the prior art (here, both references are directed to biological sensors – albeit disparate type sensors) does not, without more, teach, suggest, or provide a motivation to combine references.

<sup>3</sup> Applicants reserve the right to present the same or similar subject matter as described in any of the previously presented independent claims (or any of the previously presented dependent claims) at a later date in this application, or in a divisional application.

**Chick et al., U.S. Patent 6,040,194**

Chick describes, among other things, an in vivo "non-radiative fluorescence resonance energy transfer" (typically referred to as "FRET") based sensor for detecting the concentration of an analyte. (See Col., 2, lines 32-35). Chick describes that the efficiency of conversion of the radiation of FRET is closely dependent on the concentration of the analyte as a result of the interaction and spatial relationship of two separate components – one being an energy-absorbing donor molecule and the other being an energy-absorbing acceptor molecule. (See, for example, Col. 9, line 9 to Col. 10, line 55). Notably, Chick describes the basic elements and operation of FRET (see, for example, Col. 7, line 35 to Col. 10, line 55) and a technique to use FRET to measure glucose concentrations (see, for example, Col. 10, lines 59 to Col. 12, line 53).

The Chick technique determines the concentration of analyte based on the effect the analyte has on the efficiency of conversion of the radiation by the fluorescence reagent. (See, for example, Col. 10, lines 59 to Col. 12, line 53). Significantly, Chick does not employ (or suggest) a fluorescence reagent whose efficiency of conversion of the radiation is independent or substantially independent of the concentration of the analyte.

**Noronha et al. (U.S. Patent Application Publication US 2002/0197724)**

Noronha, to the extent understood, describes a biological sensor based on the principle of photo-induced electron transfer (often referred to as "PET"). In this regard, the Noronha sensor relies on a sensing mechanism of intramolecular photoinduced electron transfer (see, for example, Figures 4 and 5), in which part of a molecule is photoexcited and its fluorescence is quenched by an electron donor species also present in the molecule. If another chemical species, for example, a polyhydroxylated compound

(such as glucose), binds to the "surplus" electrons of the donor species of the molecule, then the quenching mechanism is limited and a fluorescence increase will be indicative of the glucose concentration.

Noronha employs a boronic acid which is bound to a polymer matrix such that, when the concentration of glucose is relatively low, a portion of the boronic acid molecule lends electrons to the fluorescent dye, thereby quenching fluorescent capability of the dye. However, when the concentration of glucose is relatively high, the glucose binds to the boronic acid which "holds" the electrons of the boronic acid molecule in place and, as such, the fluorescence of the dye is not quenched. (See, for example, paragraphs 38 and 39, and Figures 4 and 5 (and the text associated therewith)).

In certain embodiments, Noronha describe the use of a reference fluorophore. (See, for example, paragraph 84, lines 1-3). Noronha describes the reference fluorophore being covalently coupled to the same polymer matrix/composition as the fluorescent boronic acid. (Id.). Thus, Noronha describes a sensor whereby "... the fluorescent boronic acid and the reference fluorophore are covalently coupled to the polymer matrix after polymerization". (Paragraph 116 (emphasis added); see also, paragraphs 119 and 121).

Notably, Noronha states that "the reference fluorophore is selected so that it has a wavelength of excitation or emission spectrally removed from the wavelength representing the absorption maxima of the fluorophore associated with the glucose sensing boronate moieties. (Paragraph 85, lines 7-11).

Thus, Noronha describes a sensing technique (and sensor) based on photo-induced electron transfer -- an *intramolecular* phenomenon -- not FRET which is based on an *intermolecular* phenomenon. In this regard, Noronha is based entirely on the fluorophore portion of the labeled molecule being photoexcited and its fluorescence being (i) quenched

by an electron donor species also present in the molecule, and (ii) not quenched if another chemical species, such as glucose, specifically binds to the "surplus" electrons of the electron donor.

Moreover, in Noronha, the reference fluorophore is covalently bound to the same matrix/composition as the fluorescent boronic acid molecule. As such, Noronha does not employ a sensor whereby the reference fluorophore is embedded in or attached to a plurality of beads or particles which is embedded in the macroporous matrix. That is, the reference fluorophore is covalently bound to the exact same matrix/composition as the fluorescent boronic acid molecule. Accordingly, Noronha in no way teaches or suggests the use of a reference fluorophore which is embedded in or attached to a plurality of beads or particles which is embedded in the macroporous matrix.

### **Claimed Inventions**

There are many inventions described in the instant application. In an effort to present a more concise response, the discussion below will focus on only certain aspects or features of the claimed inventions. No inference of conclusion should be drawn that such aspects or features are the only reasons such claims are patentable. As mentioned above, this response is not exhaustive.

#### Amended Independent Claim 1

Amended independent claim 1 describes, among other things, an analyte sensing device for sensing a concentration of analyte in a fluid, the analyte sensing device comprises a housing and an analyte sensing component disposed in the housing. The analyte sensing component includes an analyte-specific binding ligand and a

macroporous matrix wherein the analyte-specific binding ligand is attached to the macroporous matrix.

The analyte sensing device also includes a first radiation converting component and a second radiation converting component. The second radiation converting component converts radiation of a second wavelength to radiation having at least one wavelength that is different from the second wavelength. The efficiency of conversion of the radiation of the second wavelength by the second radiation converting component is independent or substantially independent of the concentration of the analyte in the housing.

In addition, analyte sensing device of amended claim 1 further includes a plurality of beads or particles, wherein the second radiation converting component is embedded in or attached to at least one of the plurality of beads or particles. Moreover, the plurality of beads or particles is embedded in the macroporous matrix.

#### Amended Independent Claim 71

Amended independent claim 71 describes, among other things, an analyte sensing system including an analyte sensing device, like that set forth in amended claim 1, and (i) a radiation providing unit to provide radiation at the first wavelength and (ii) a radiation detecting unit to detect the radiation of one or more wavelengths including the radiation of the at least one wavelength that is different from the first and second wavelengths and output data which is representative of the intensity of the radiation of the at least one wavelength emitted by the first and second radiation converting components.

#### Amended Independent Claim 102

Amended independent claim 102 describes, among other things, an analyte sensing device for sensing a concentration of analyte in a fluid, the analyte sensing

device comprises a housing and an analyte sensing component disposed in the housing. The analyte sensing component includes an analyte-specific binding ligand and a macroporous matrix wherein the analyte-specific binding ligand is attached to the macroporous matrix. The analyte sensing component also includes a plurality of beads or particles which is disposed or embedded in the macroporous matrix.

Further, the analyte sensing component includes a first radiation converting component and a second radiation converting component. The second radiation converting component converts radiation of a second wavelength. The efficiency of conversion of the radiation of the second wavelength by the second radiation converting component is independent or substantially independent of the concentration of analyte in the housing.

Amended independent claim 102 further recites that the second radiation converting component is embedded in or attached to at least one of the plurality of beads or particles. As mentioned above, the plurality of beads or particles is disposed or embedded in the macroporous matrix.

**Chick in view of Noronha Does NOT  
Render Obvious the Claimed Inventions**

Simply put, Chick in view of Noronha does not render obvious the claimed inventions. First, there is no teaching or suggestion (for example, in Chick or Noronha) that a person of ordinary skill in the art would or could substitute the reference fluorophore of the PET sensing technique and sensor of Noronha into the FRET sensing technique and sensor of Chick. A general relationship between prior art (here, both Chick and Noronha are directed to biological sensors – albeit very different) does not, without more, teach, suggest or provide a motivation to combine the references. Chick and Noronha employ

very different sensing techniques. The operation and characteristics/response of such sensors are considerably different. Thus, because both Chick and Noronha describe biological sensors using fluorophores does not, without more, motivate one skilled in the art to substitute selected features of the Noronha sensor into the Chick sensor. Furthermore, the device/technique of Chick and Noronha, as taught, are not combinable to attain a reference fluorophore whose fluorescence is substantially independent of glucose concentration because while the configuration disclosed by Noronha is compatible with the PET fluorescence mechanism, it is incompatible with the FRET mechanism employed in the Chick device/technique.

However, even assuming, for the sake of argument, that one skilled in the art (at the time of the invention) would combine Chick and Noronha as stated in the Office Action, the amended claims of the instant application are not obvious because there is no teaching or suggestion of a sensor including (i) a plurality of beads or particles which is embedded in the macroporous matrix, and (ii) the second radiation converting component being embedded in or attached to at least one of the plurality of beads or particles. That is, neither Chick nor Noronha, alone or in combination, teach or suggest (or motivate one skilled in the art to provide) a sensor including a plurality of beads or particles which is embedded in the macroporous matrix wherein the second radiation converting component is embedded in or attached to at least one of the plurality of beads or particles.<sup>4</sup>

Although the Chick device is based on a FRET sensing technique, Chick neither teaches nor suggests implementing a fluorescence reagent to convert radiation of a

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<sup>4</sup> Notably, the shortcomings of Chick and Noronha, as described in these remarks, are equally applicable to amended independent claims 71 and 102.



second wavelength to at least one wavelength that is different from the second wavelength wherein the efficiency of conversion is independent or substantially independent of the concentration of the analyte in the housing. (See, for example, amended claim 1). Moreover, there is absolutely no teaching or suggestion in Chick to provide a plurality of beads or particles which is embedded in the macroporous matrix wherein the second radiation converting component is embedded in or attached to at least one of the plurality of beads or particles.<sup>5</sup>

Noronha provides no help in this regard. Noronha describes a sensing technique and sensor based on photo-induced electron transfer which is an *intramolecular* phenomenon -- not FRET which is based on an *intermolecular* phenomenon. Thus, in Noronha, the reference fluorophore is covalently bound to the exact same matrix/composition as the fluorescent boronic acid molecule. As such, Noronha does not employ a sensor whereby the reference fluorophore is embedded in or attached to a plurality of beads or particles which is embedded in the macroporous matrix. That is, the reference fluorophore is covalently bound to the exact same matrix/composition as the fluorescent boronic acid molecule. Accordingly, Noronha in no way teaches or suggests

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<sup>5</sup> Indeed, there is absolutely no suggestion or motivation to one skilled in the art to modify Chick in such a way as to implement fluorescence reagents having an efficiency of conversion (of radiation of a wavelength to radiation of another wavelength) that is independent of the concentration of the analyte being detected. The Chick device and technique is based solely on fluorescence reagent having an efficiency of conversion of radiation of a first wavelength to another wavelength which is dependent on the concentration of the analyte. As such, Chick neither contemplates nor motivates one skilled in the art to include a fluorescence reagent having an efficiency of conversion which is independent of the concentration of the analyte.

the use of a reference fluorophore which is embedded in or attached to a plurality of beads or particles which is embedded in the macroporous matrix.

In addition, there is absolutely no suggestion or motivation to one skilled in the art to modify Noronha or Chick to implement a reference fluorophore which is embedded in or attached to a plurality of beads or particles which is embedded in the macroporous matrix. Indeed, Noronha *teaches away* from such an approach since the reference fluorophore of Noronha is intended to mimic the environment of the other fluorophore (the fluorophore affected by the analyte. (See, Noronha, for example, paragraph 84, lines 1-6). In order to provide the analogous environment, the reference fluorophore and the fluorescent boronic acid molecule are covalently bound to the exact same matrix/composition. (See, Noronha, for example, paragraph 87, lines 1-5, and paragraphs 116, 119 and 121). Thus, Noronha teaches away from employing a reference fluorophore which is embedded in or attached to a plurality of beads or particles which is embedded in the macroporous matrix.<sup>6</sup>

In sum, Chick and Noronha, alone or in combination with the other cited art, do not render the claimed inventions obvious. There is no teaching or suggestion in either Chick or Noronha that a person of ordinary skill in the art would or could substitute the reference fluorophore of the PET system/sensor of Noronha into the FRET system/sensor of Chick. Moreover, even if one skilled in the art incorporated the reference fluorophore of Noronha

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<sup>6</sup> Further, in the Noronha sensor/system, “the wavelength of excitation or emission [of the reference fluorophore is] spectrally removed from the wavelength representing the absorption maxima of the fluorophore associated with the glucose sensing ... moieties. (Noronha, paragraph 85, lines 7-11). However, the Chick sensor/system detects a single wavelength. Presumably, Chick would employ same excitation wavelengths for the dyes. Under these circumstances, a Noronha reference fluorophore would be incompatible with the Chick sensor because it would not have a suitable excitation wavelength.

into the FRET system/sensor of Chick, there is no teaching or suggestion (or motivation to one skilled in the art) to implement a reference fluorophore which is embedded in or attached to a plurality of beads or particles which is embedded in the macroporous matrix.

### **Dependent Claims**

As mentioned above, for the sake of brevity, this response does not present the additional reasons/bases that the dependent claims are patentable over Chick and/or Noronha. Those reasons/bases are numerous. However, for at least the reasons stated above, it is respectfully submitted that the dependent claims are patentable in view of Chick and/or Noronha, either alone or in combination.

### **Rejection based on Personal Knowledge of the Examiner**

Pursuant to 37 CFR §104(d)(2), to the extent the Examiner relies on her own personal knowledge, Applicants respectfully request that she support her personal knowledge by affidavit. For example, the Examiner has provided or identified no evidence (for example, teaching or suggestion in the prior art) for the proposition that "it would have been obvious to one having ordinary skill art ... to include in the device of Chick et al., a radiation converting component wherein the efficiency of conversion is independent of the concentration of analyte as taught by Noronha et al., in order to provide an internal referencing system to correct for background fluorescent signals and cancel out changes in fluorescence intensity." (Office Action, pages 4-5). As mentioned above, Noronha describes a sensing technique and sensor based on photo-induced electron transfer -- an *intramolecular* phenomenon -- not FRET which is based on an *intermolecular* phenomenon. Chick and Noronha employ very different and incompatible sensing techniques. The operation of the sensors is considerably different. In addition, the

characteristics/response of the sensors to the presence of analyte is considerably different.

Stated simply, implementation of the reference fluorophore as taught by Noronha into the device/technique of Chick would not result in a fluorophore whose fluorescence was independent or substantially independent of the analyte concentration since FRET would likely occur between the reference dye and other sensing components.

While it is true that both Chick and Noronha describe biological sensors employing fluorophores – albeit quite different, there is no teaching or suggestion that the reference fluorophore of PET sensor of Noronha could be employed in the FRET sensor of Chick. Because both Chick and Noronha describe biological sensors using fluorophores does not, without more, motivate one skilled in the art to substitute selected features of Noronha into the Chick sensor. The general relationship between references is, by itself, insufficient to suggest a motivation to combine the references. Moreover, such a generation relationship is not a substitute for a motivation or suggestion to combine the references.

In sum, to the extent the Examiner relies on her own personal knowledge regarding the above mentioned statements/assertions, which appears to be the case, Applicants respectfully request that she support her personal knowledge by affidavit. Obviously, no inference or conclusion should be drawn that Applicants agree, in any way, with such assertions.

#### **Other Rejections in the Office Action**

No inference or conclusion should be drawn that Applicants agree, in any way, with the rejections set forth in the Office Action – even where such rejections are not particularly, individually and/or specifically addressed herein. Indeed, Applicants do not

agree. However, in an effort to provide a more concise response, Applicants do not comment on such rejections.<sup>7</sup>

Notably, no inference or conclusion should be drawn that Applicants believe that the previously pending claims (independent or dependent) were unpatentable in view of the instant amendment.

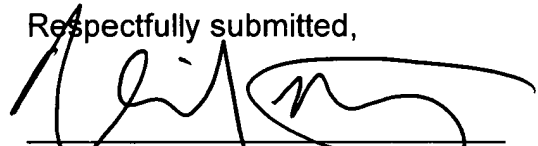
### CONCLUSION

Applicants respectfully request entry of the foregoing amendments and reconsideration of the instant application. Applicants submit that all of the pending claims present patentable subject matter and allowance of the claims is respectfully requested.

It is noted that should a telephone interview expedite the prosecution of this application in any way, the Examiner is invited to contact the undersigned at the telephone number listed below.

Date: April 4, 2006

Respectfully submitted,



Neil A. Steinberg, Reg. No. 34,735  
Telephone No. 650-968-8079

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<sup>7</sup> The Office Action combines features of Chick, Noronha and other patents without consideration that the Chick, Noronha and other patents are largely based on very different/diverse sensing techniques. There is no evidence of motivation to combine selected features of Chick with selected features of Noronha (or the other patents identified in the Office Action) as set forth in the rejections. Indeed, as discussed above, Chick and Noronha employ different types of sensing techniques whereby the sensors, and the constituent parts thereof, behave/respond quite differently in the presence of analyte.